
(12) UK Patent Application (19) GB (11) 2 009 698 A

(21) Application No 7848043

(22) Date of filing

12 Dec 1978

(23) Claims filed

12 Dec 1978

(30) Priority data

(31) 51842/77

(32) 13 Dec 1977

(33) United Kingdom (GB)

(43) Application published

20 Jun 1979

(51) INT CL² B01J 13/02

(52) Domestic classification

B8C A

B1V 109 110 111 112

210 211 301 D

(56) Documents cited

US 3819838A

(58) Field of search

B1V

B8C

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(54) Microcapsules

(57) Microcapsules are prepared encapsulated by a film containing at least three alternating layers of hydrophilic and hydrophobic colloid materials. Suitable hydrophilic colloids include polysaccharides and proteins. Suitable hydrophobic colloids include polychloroprene, polyvinyl chloride and similar polymers. They may be prepared by inverting emulsions of the oil-in-water type to form duplex emulsions of the other type and vice versa. They are useful in agriculture, biochemistry and pharmacy.

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SPECIFICATION

Preparation of emulsions

- 5 This invention relates to microcapsules and their preparation.

Microcapsules are small capsules, usually spherical or spheroidal in shape and usually in the size range 100 nanometers to 100 microns in diameter. They can be in the form of a sponge-like matrix with tortuosities occupying the whole of the sphere or spheroid or alternatively they can comprise a shell surrounding a liquid, or possibly solid, core.

- 15 Microcapsules have been prepared from simple emulsions with one- or at most two-ply side walls enclosing the core. Such microcapsules have a limited range of retention of soluble materials in the core. This is due to the fact that the walls of such capsules are likely to be totally hydrophilic or hydrophobic in nature. They also have limited use in aqueous media (either internal or external) at extremes of pH because the mechanical stability of the hydrophilic colloid component of the wall is effective only over a limited pH range.

We have now surprisingly discovered that microcapsules prepared from a duplex emulsion possess films in which hydrophobic and hydrophilic colloids interact to furnish multilayered interfacial films of viscosity much greater than films of either component alone.

Thus according to the present invention there are provided microcapsules encapsulated by a film containing at least three alternating layers of hydrophilic and hydrophobic colloid materials.

Suitable hydrophilic colloid materials include water-soluble polysaccharides such as gum acacia, alginates and cellulose ethers and proteins such as gelatin and casein.

Suitable hydrophobic colloid materials include polychloroprene, polyvinyl chloride, acrylonitrile-butadiene-styrene copolymer, poly-acrylonitrile and water-insoluble cellulose esters.

In some cases, the use of a mutual solvent such as acetone may be necessary with substances which are sparingly soluble in oil.

50 According to another aspect of the present invention, there is provided method for the preparation of microcapsules encapsulated by a film containing at least three alternating layers of hydrophilic and hydrophobic colloid materials which method comprises the steps of

- (a) forming a solution of a hydrophilic colloid in water, forming a solution of a hydrophobic colloid in a non-aqueous water-immiscible solvent hereinafter referred to as "oil" and emulsifying the solutions together to form a water-in-oil emulsion, and
- (b) further emulsifying the resulting water-in-oil emulsion with a further quantity of the

solution of the hydrophilic colloid in water to form a "water-in-oil"-in-water duplex emulsion.

- 70 In order firmly to bond the interfacial layers, the oil is preferably removed from the oil-in-water emulsion.

Alternatively, according to another aspect of the invention, there is provided a method for the preparation of microcapsules encapsulated by a film containing at least three alternating layers of hydrophilic and hydrophobic colloid materials which method comprises the steps of

- (a) forming a solution of a hydrophobic colloid in oil, forming a solution of a hydrophilic colloid in water and emulsifying the solutions together to form an oil-in-water emulsion, and
- (b) further emulsifying the resulting oil-in-water emulsion with a further quantity of the solution of the hydrophobic colloid in oil to form an "oil-in-water"-in-oil duplex emulsion.

80 In this alternative, in order firmly to bond the interfacial layers, the water is preferably removed from the water-in-oil emulsion.

The oil and water may be removed from the respective water-in-oil-in-water and oil-in-water-in-oil duplex emulsions by conventional methods such as the application of heat, the reduction of pressure or, simply, evaporation under ambient conditions.

Suitable water-immiscible oils include hydrocarbons such as paraffins, naphthenes and aromatics, either as individual compounds or in mixtures such as light petroleum fractions; esters and halogenated hydrocarbons, although especial care must be taken in connection with the use of the latter since hazards may arise in certain circumstances known to those skilled in the art.

Suitable concentrations of colloidal material in water and oil are in the range 0.1% to 10% w/v.

110 When the oil in the first case is removed from Stage (b), microcapsules are provided comprising plies of alternate hydrophilic, hydrophobic and hydrophilic components. Correspondingly, when the water in the second case is removed from Stage (b), microcapsules are provided comprising plies of alternate hydrophobic, hydrophilic and hydrophobic components. The plies are firmly bonded together and are stable even under strongly acid or alkaline conditions.

The wall thickness of the central ply can be controlled during the manufacturing process by varying the concentration of the colloidal material, the temperature, relative phase volumes, etc. This provides the microcapsules with a wide range of release characteristics.

Ambient temperature and pressure generally provide satisfactory preparative conditions for the emulsification stages.

130 If desired, additional layers of hydrophilic

and hydrophobic colloids can be built up by further stages in which the emulsions are inverted from the previous stage.

The continuous phase from the last emulsion stage may be evaporated to produce the microcapsules in the form of a free flowing powder.

Microcapsules are suitable for use as slow release fertilisers and for biochemical and pharmaceutical purposes when appropriate active compounds are encapsulated. For pharmaceutical use, the materials of construction must, of course, be non-toxic and non-irritant.

The invention is illustrated with reference to the following Examples.

Example 1

Acacia/Polychloroprene

The following solutions were first prepared:—

(1) 100 mls of:—

0.5% w/v crystal violet

5.0% w/v gum acacia senegal in distilled water.

(2) 100 mls of:—

4% w/v polychloroprene manufactured by Distugil S.A. as Grade MC 30 in toluene.

The crystal violet was used simply as a visual marker. 10 mls of (1) were then emulsified in 10 mls of (2), using a Silverson Model 407 Mixer fitted with a $\frac{1}{2}$ inch diameter mixing head to form a water-in-oil emulsion. The mixer was operated at maximum speed for 3 minutes and the solution (1) was introduced slowly drop-wise during this period. The product was called (3).

In the second stage 20 mls of (3) were slowly, drop-wise, emulsified in 20 mls of (1) without the crystal violet to give an oil-in-water emulsion (4), over a 3 minute period.

The central polychloroprene section of the walls of the microcapsules, so formed in (4), was then stabilised by slowly agitating the product until all traces of toluene had evaporated.

The initial size distribution of the microcapsules formed was investigated using a Coulter Counter Model A fitted with a 100 micron orifice tube.

The test sample was prepared by diluting emulsion (4), 1:100 with distilled water and then 1:100 with 0.9% w/v sodium chloride as a counting solution. The particle size distribution so obtained was:—

	Coulter Diameter Microns	Cumulative Weight Percentage Oversize
	19.88	0.00
55	13.31	2.56
	10.57	13.47
	8.40	22.70
	6.68	40.63
	5.33	51.15
60	4.27	18.16
	3.45	87.68
	2.83	93.51
	2.39	97.54
	2.12	100.00
65		

Example 2

Acacia/Cellulose Acetate-Phthalate

The following solutions were first prepared:—

(1) 100 mls of:—

0.5% w/v crystal violet

5.0% w/v gum acacia senegal in distilled water

(2) A solution consisting of:—

5 g cellulose acetate-phthalate

40 ml acetone

60 ml ethyl acetate

Cellulose acetate-phthalate is not readily soluble in ethyl acetate and it was first dissolved in the acetone and then the ethyl acetate was added.

The method of preparation of the microcapsules was the same as for Example 1.

CLAIMS

1. Microcapsules encapsulated by a film containing at least three alternating layers of hydrophilic and hydrophobic colloid materials.
2. Microcapsules according to Claim 1 comprising plies of alternate hydrophilic, hydrophobic and hydrophilic components.
3. Microcapsules according to Claim 1 comprising plies of alternate hydrophobic, hydrophilic and hydrophobic components.
4. Microcapsules according to any of the preceding claims wherein the hydrophilic colloid is a water soluble polysaccharide.
5. Microcapsules according to Claim 4 wherein the water soluble polysaccharide is gum acacia, an alginate or a cellulose ether.
6. Microcapsules according to Claim 3 wherein the hydrophilic colloid is a protein.
7. Microcapsules according to Claim 6 wherein the protein is gelatin or casein.
8. Microcapsules according to any of the preceding claims wherein the hydrophobic colloid is polychloroprene, polyvinyl chloride, acrylonitrile-butadiene-styrene copolymer, polyacrylonitrile or a water-insoluble cellulose ester.
9. A method for the preparation of microcapsules encapsulated by a film containing at least three alternating layers of hydrophilic

and hydrophobic colloid materials which method comprises the steps of

- 5 (a) forming a solution of a hydrophilic colloid in water, forming a solution of hydrophobic colloid in a non-aqueous water-immiscible solvent hereinafter referred to as "oil" and emulsifying the solutions together to form a water-in-oil emulsion, and
- 10 (b) further emulsifying the resulting water-in-oil emulsion with a further quantity of the solution of the hydrophilic colloid in water to form a "water-in-oil"-in-water duplex emulsion.

10. A method according to Claim 9 wherein the oil is removed from the oil-in-water emulsion.

11. A method for the preparation of microcapsules encapsulated by a film containing at least three alternating layers of hydrophilic and hydrophobic colloid materials which method comprises the steps of

- 20 (a) forming a solution of a hydrophobic colloid in oil, forming a solution of a hydrophilic colloid in water and emulsifying the solutions together to form an oil-in-water emulsion, and
- 25 (b) further emulsifying the resulting oil-in-water emulsion with a further quantity of the solution of the hydrophobic colloid in oil to form an "oil-in-water"-in-oil duplex emulsion.

12. A method according to Claim 11 wherein the water is removed from the water-in-oil emulsion.

35 13. A method according to any of Claims 9 to 12 wherein the water-immiscible oil is a hydrocarbon, an ester or a halogenated hydrocarbon.

40 14. A method according to any of Claims 9 to 13 wherein the concentrations of colloidal material in water and oil are in the range 0.1% to 10% w/v.

15. A method for the preparation of microcapsules as hereinbefore described with reference to the Examples.

45 16. Microcapsules whenever prepared by a process according to any of Claims 9 to 16.